Chapter

Novel Techniques in the Assessment of Sports-Related Traumatic Brain Injury

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Abstract

Mild traumatic brain injuries (mTBI) or concussions are a substantial health concern, particularly in collision and contact sports. Consequently, there is growing concern regarding the acute and chronic effects of repeated brain trauma. Traditional assessment of mTBI has been based on clinical or computed tomography (CT) assessments followed by a period of in-hospital observation in some cases. These may have significant time and cost implications while potentially exposing patients to ionizing radiation and providing a low sensitivity and specificity. Recent advancements have focused on novel modalities that may potentially predict early and long-term sequelae from mTBI with greater accuracy and provide the optimum personalized treatment plan in collaboration with the athlete. This chapter will outline state of the art in these modalities, from salivary and blood biomarkers imaging and neuropsychology assessments, and discuss their translational applicability to the clinical setting.

Keywords: concussion, sports, head injury, neuroimaging, biomarker, return to play

1. Introduction

Traumatic brain injury (TBI) is a leading global cause of mortality and morbidity, with an estimated 69 million people globally suffering from TBI annually. The leading mode of injury in TBI is road traffic accidents, with the Western Pacific and Southeast Asia experiencing the highest global disease burden [1]. TBI may be categorized by severity in correlation to the Glasgow Coma Scale (GCS), with 'mild' TBI defined as GCS 13-15, 'moderate' TBI as GCS 9-12, and 'severe' TBI as GCS 3-8. This is clinically relevant as mortality varies from 0.1% in mild TBI to 40% in severe TBI [2, 3], although up to 90% of all TBI is mild [4].

Mild TBI (mTBI), which is used interchangeably with 'concussion', has been further defined with four-point criteria by the American Congress of Rehabilitation Medicine (ACRM) [5]. The management of mTBI varies globally but may involve hospital admission for observation or a CT head scan based on established criteria, such as the Canadian CT head rule [6, 7], with subsequent neurosurgical management if indicated. However, the vast majority of mTBI cases have normal neuroimaging studies, while a normal CT head does not rule out mTBI. Therefore, existing diagnostic pathways may underestimate the degree of tissue insult and subsequent neurological

dysfunction, simultaneously having time and cost implications and potentially subjecting the patient to ionizing radiation [8].

Sports-related concussion (SRC) is a recognized type of TBI, defined by the Concussion in Sport Group (CISG) as 'a direct blow to the head, neck or body resulting in an impulsive force being transmitted to the brain that occurs in sports and exercise-related activities' [9]. The risk is higher in contact sports, such as boxing, American football, ice hockey, association football, rugby, and martial arts, as well as high-velocity sports, such as cycling, motor racing, equestrian sports, rodeo, skiing, and roller skating [10]. SRC may cause acute injuries akin to other modes of TBI. However, there is increasing recognition of the chronic sequelae of SRC, such as chronic traumatic encephalopathy (CTE – usually resulting from repetitive long-term mTBI events) and posttraumatic parkinsonism. Moreover, there is an association with the development of neurodegenerative diseases such as Alzheimer's disease, Motor Neuron Disease (MND), or Parkinson's disease [11]. Increasing awareness of these chronic sequelae has contributed to wider public interest in SRC over the past decade. Thus, optimal assessment and management of SRC is a public health concern.

1.1 Current methods of assessing and managing sports-related concussion

At present, there is no objective test to diagnose concussion. Assessment is, therefore, primarily based on clinical assessment and athletes' self-reported symptoms. Consequently, pitchside concussion assessment, investigations, and return-to-play protocols vary between organizations and countries. Commonly used pitchside tools include the Sport Concussion Assessment Tool (SCAT), incorporating clinical measures such as GCS, cognitive assessments such as the Maddocks Score, and a modified Balance Error Scoring System (BESS) [12].

The philosophy in managing SRC traditionally centers around a brief symptom-free period of physical and cognitive rest before allowing the athlete to engage in a graduated return to play [13]. This is usually 1-4 weeks [14]; however, the updated CISG consensus guidelines recommend 'relative rest' including activities of daily living and reduced screen time for up to 2 days following concussion; a return to light-intensity physical activity (e.g., walking) is recommended within 24-48 hours of injury, followed by advancing the duration and intensity of physical activity while monitoring for any recurrence of concussion-related symptoms [9]. Concussion substitutes have been successfully trialled in professional soccer, cricket, and rugby [15–17] to minimize disruption to the sporting spectacle.

However, the reliance on clinical symptoms likely underestimates the impact of SRC on athletes. Athletes may not be aware of the symptoms of SRC and may be motivated to under-report their symptoms to avoid sporting or financial loss [18]. Several assessments require a period of baseline and follow-up testing and formal neuropsychological evaluation, which may not be accessible to sporting clubs with limited resources.

Therefore, a more accurate pitchside and clinical assessment of SRC is needed to provide more individualized care to athletes suffering from this concussion. In this chapter, we will discuss the main emerging domains in the assessment of SRC: biomarkers (blood and salivary), neuro-imaging, and neurocognitive assessment. We will then discuss the implications of these novel modalities on return to play for athletes.

2. Biomarkers

Biomarkers are objective, quantifiable characteristics of biological processes [19] and usually refer to measurable biological compounds with a purported or established relationship with a clinical endpoint. An ideal biomarker in SRC would be highly sensitive, specific, easily measurable, and correlate with the clinical syndrome several days after the initial injury, given the practicalities of arranging patient sampling and analysis. Although there has been increasing interest in the field over the last decade, no FDA-approved biomarkers are in routine clinical use. Therefore, in this section, we will review several promising biomarker candidates that may have future utility in the assessment of SRC. Given the comparative inaccessibility in obtaining cerebrospinal fluid (CSF), it is unlikely to be a practical biomarker in SRC and therefore is not further considered in this chapter.

2.1 Blood biomarkers

Blood (serum and plasma) biomarkers of SRC – and, more widely, brain injury – must be considered in the context of the biomarker's ability to cross the blood-brain barrier into the systemic circulation, as well as whether the marker is produced extracranially. Nevertheless, several biomarkers have emerged in the literature.

2.1.1 S100β

S100**β** is a calcium-binding protein responsible for intracellular calcium regulation in astrocytes and is considered a marker of astrocyte injury [20]. It is also found in adipose tissue, muscle, and skin [21]. This marker has been extensively studied in large populations of TBI of all severities, being raised in patients with traumatic cerebral edema and contusions compared to other types of traumatic intracranial hemorrhage. Moreover, S100**β** levels are significantly lower in concussion than all intracranial bleeds [22]. Subsequently, Scandinavian head injury guidelines have included S100**β** as a screening test to obviate the need for CT head in selected patients if sampled within 6 hours of injury [23].

However, results with S100**β** in athletes are mixed. S100**β** has been raised following boxing, running, swimming, association football, ice hockey, and basketball [24] compared to before the sporting activity, which may be partially explained due to its secretion from known extra-cranial sites during exercise. There is also some association with head injury sustained during sporting activity: in one study, increased levels of S100**β** were found following heading and 'acceleration-deceleration' trauma during male professional association football games but was not associated with the high Rivermead postconcussion questionnaire scores taken 24-48 postmatch [25]. Moreover, another study found a significant increase in S100**β** in amateur male boxers who predominantly received punches to the head versus punches to the body, along with increases in Neuron-Specific Elastase (NSE), creatine kinase (CK) and cortisol [26].

Timing of S100**β** sampling is an important consideration, given its concentration peaks up to 1 hour following injury, falling back to baseline up to 6 days following injury [27]. In a recent cohort study of professional rugby players in France, the degree of change of S100**β** (along with NFL) at 36 hours postinjury compared to the preseason baseline was significantly associated with nonresolving concussion, while

the raw concentrations of each biomarker did not demonstrate any significant difference between those with or without nonresolving concussion [28].

In summary, it appears that S100**β** has a positive association with structural abnormalities in patients with SRC, with some association with postconcussion syndrome in the acute stage. Thus, it may have a role in the acute evaluation of SRC.

2.1.2 GFAP

Glial fibrillary acidic protein is a monomeric intermediate protein found in the astroglial skeleton in gray and white matter [20]. It has also demonstrated utility in detecting neuroimaging abnormalities, superior to S100**β** in predicting the presence of traumatic intracranial lesions on CT in patients with mild to moderate TBI [29] and axonal injury on magnetic resonance imaging (MRI) 3 months postinjury in an mTBI population [30].

Although GFAP has been less assessed in the SRC literature, two studies illustrate its potential role as a biomarker. Firstly, a prospective cohort study found a significantly higher concentration of GFAP (alongside NFL) in the CSF of Olympic boxers 1-6 days following a bout and also following a 14-day rest period compared to controls. The one boxer who reported a concussion had the highest GFAP concentration at both time points, suggesting a potential role as a marker of subclinical concussion [31]. Moreover, a large multi-center case-control study of 504 college athletes with concussion found that serum GFAP was significantly elevated acutely following injury up to 7 days following return to play compared to preseason baseline and up to 24-28 h following injury compared to contact and noncontact sports controls. Moreover, GFAP was also significantly elevated in athletes who had a loss of consciousness (LOC) or posttraumatic amnesia (PTA) from the point of injury up to the point of athletes reporting to be asymptomatic and undergoing return to play protocols [32]. Interestingly, the area under the curve (AUC) for GFAP in differentiating between concussed athletes and contact- and noncontact sport athletes was inferior to the SCAT-3 assessment (0.67 to 0.68 vs. 0.94 to 0.95). However, it had a greater AUC in differentiating between concussed athletes with LOC/PTA (0.81 v 0.54 for SCAT-3).

These studies suggest that GFAP may be a marker of the severity of SRC, with some relationship between SRC symptomatology and severity.

2.1.3 Tau

Tau is an intracellular, microtubule-associated protein responsible for assembling axonal bundles. There is a recognition of aggregation and misfolding of tau being responsible for the development of 'tauopathies', a family of neurodegenerative conditions which includes CTE [33]. It has also been found in the liver, kidney, and testes [34]. Tau predicts poor outcomes in severe head injury, akin to S100**β** and GFAP [20], with CSF concentrations of cleaved-tau and total tau having particularly strong associations [35–37]. However, its role in mTBI is more uncertain, where it was shown not to correlate with the long-term outcome (at 3 months) [38], postconcussion syndrome [39], or traumatic intracranial lesions on CT [40].

Moreover, there have also been mixed results in the SRC-related literature. One study in 28 ice-hockey players found total tau (t-tau) levels to be significantly raised in players who suffered a concussion compared to a preseason baseline, along with S100**β**. However, only t-tau levels at 1 h postconcussion were predictive of the length

of resolution of concussive symptoms (AUC 0.91), while high t-tau 144 h post-concussion was associated with the persistence of postconcussion syndrome [27]. However, serum t-tau was found to be elevated in a study of 30 Olympic boxers following a bout compared to 25 controls, even though none of the boxers had a concussion [41]. CSF t-tau was also elevated in this boxer cohort but was not correlated with serum levels [31].

T-tau has also provided mixed results assessed in two large cohort studies: in a 2017 study of 623 collegiate athletes (46 SRC), serum t-tau was found to be significantly higher in SRC and athlete controls compared to nonathlete controls, while elevated t-tau from 6 to 72 h postconcussion was associated with a long return-to-play period (defined as >10 days), with 6-hour t-tau having a high predictive value for a long RTP (AUC 0.81) [42]. In another 2020 study of 1760 collegiate athletes (264 SRC), tau was significantly elevated at 1 h postinjury compared to preseason baseline (along with GFAP and UCH-L1) but returned to baseline after this time point. Moreover, there was no association or predictive value for tau in return to play in athletes who suffered LOC/PTA [32].

The exact significance of elevated tau, therefore, remains to be determined. Like GFAP and S100**β**, it is a marker of brain injury with strong associations in severe TBI, but there is conflicting data in the literature about its utility. This may be explained by methodological differences in the studies concerned, particularly given the 1 h peak of t-tau postconcussion, but more robust data is required.

2.1.4 Other blood biomarkers

Several other biomarkers have been studied in the literature, including markers of neuronal (neuronal-specific elastase (NSE), brain-derived neuronal factor (BDNF) and UCH-L1), axonal (alpha-II spectrin and neurofilament light) and blood-brain barrier (CSF: serum albumin ratio) dysfunction [43]. High NFL has been correlated with SRC with LOC/PTA even beyond clinical recovery in collegiate athletes [32]. It has correlated with symptom severity, long RTP, and even retirement (if high at 144 h postinjury) for ice hockey players who had PCS symptoms >1 year [44]. This biomarker outperformed tau, S100**β** and NSE and, therefore could be considered a marker of severe PCS.

In summary, blood biomarkers representing various structural components of the CNS have emerged in the literature, with early applications in mTBI and SRC. Of all these, S100**β**, GFAP, tau, and NFL have emerged as leading candidates, and their future diagnostic utility likely lies in the combined use of these markers [32].

2.2 microRNAs

In contrast to the biomarkers already discussed, microRNA (miRNA) are smaller, being 19-28 nucleotides in size. They are a class of endogenous, noncoding RNA regulating messenger RNA (mRNA) expression. It is thought that they contribute to the development, differentiation, and synaptic plasticity of neurons, although their function is not fully understood. They are stable at variable pH conditions and resistant to freeze-thawing and enzymatic environmental changes [45]. Over the past decade, there has been increasing research on the utility of miRNA as biomarkers of a range of neurological disorders [46].

Consequently, several research groups have trialed varying panels of miRNA in TBI. One of the first such studies in 2010 found that a combination of serum miR-16,

miR-92a, and miR-765 had a 100% sensitivity and specificity for identifying patients with severe TBI compared to healthy volunteers or orthopedic trauma patients [47]. A further study identified ten miRNA molecules that were upregulated in both mild/moderate TBI and severe TBI [45]. Concentrations of four of these molecules, miR-328, miR-362-3p, miR-451, and miR-486 were also significantly upregulated in the CSF of this cohort, with changes in concentration in eight of these markers being significantly associated with traumatic intracranial lesions on CT scan. AUC >80% for predicting TBI was found in five miRNA molecules, highest in miR-92a (AUC 0.86).

In a cohort study of collegiate American football players throughout a season, serum miRNA concentrations were assessed against indications of concussion, subconcussive impacts, and neurocognitive function [48]. All athletes in this study had a significantly higher concentration of a panel of preselected miRNA biomarkers compared to controls. When considering the Standard Assessment of Concussion (SAC) clinical assessment, five biomarkers had a high predictive value for low SAC scores (<28), with miR-195 having the best predictive value (AUC 0.90). miR-195 was also significantly predictive of concussion in the two athletes (2%) who had suffered this, with an AUC of 0.92, equal to miR-92a. Moreover, neurocognitive scores showed a significant negative correlation with miR-505, miR-30d, miR-92, and miR-151-5p. Worsening balance was significantly correlated with miR 505, miR-30d, miR-151-5p, and worsening reaction times were significantly worsened with miR-20a, miR-505, miR-30d, miR-92, and miR-151-5p.

Another paradigm in the field has been the exploration of salivary miRNA biomarkers. The discovery of neurodegenerative markers such as tau [49], alpha-synuclein and DJ-1 [50] have sparked interest in markers of TBI in saliva. The ease of collecting and storing saliva makes it ideal as a point-of-care test. One group identified five salivary miRNA candidates upregulated in athletes with SRC [51]. One marker, let-7i-5p, had an AUC of 0.86 in predicting SRC.

Interestingly, all miRNA markers were also expressed in all tissues but were highest in the brain. There was also a significantly positive correlation between let-7i-5p and miR-27b-3p and percentile on the Immediate Postconcussion Assessment Cognitive Test (ImPACT) concussion assessment tool. Finally, miR-135b-5p was inversely correlated with the number of concussions. This has progressed to a panel of miRNA (salivary small noncoding RNA – sncRNA) retrospectively and prospectively predicting concussion in a cohort of rugby union players using a panel of 14 sncRNA biomarkers to a high degree of accuracy (AUC 0.96 1 h postgame, 0.93 36-48 h postgame) [52].

The interest in miRNA in SRC has circled back to the civilian population, with a prospective observational cohort study aiming to assess 23 salivary miRNA biomarkers in nonathletes admitted from the emergency department with maxillofacial trauma with a concomitant concussion, compared to those admitted for orthopedic trauma [53].

In summary, microRNA has represented a significant advancement in the diagnosis of SRC, being an easy-to-administer investigation that shows high sensitivity and specificity in diagnosing SRC, with some correlation to neuropsychological measures. Further validation of miRNA is required in longer-term follow-up studies and in return to play scenarios.

2.3 Imaging

Imaging forms a key pillar in the investigation of all forms of TBI. There is a general international consensus on the indications for CT head scanning following

acute TBI [23]. However, using these criteria, most cases of mTBI, and by extension SRC, would not undergo a CT scan, and most CT heads would fail to show any acute abnormalities. As seen in the previous section, where there are structural changes in CT, this has been correlated with higher levels of biomarkers of CNS injury and miRNA. This may not be specific in detecting subtle structural and functional imaging abnormalities in an SRC cohort. For this purpose, magnetic resonance imaging (MRI) is an alternative modality that may yield radiological biomarkers in SRC. Currently, American neuroradiology guidelines do not recommend MRI for routine clinical evaluation of TBI, and there are no approved radiological biomarkers [54]. However, there are emerging potential MRI techniques that have yielded biomarkers that may have a role in SRC.

2.3.1 Structural MRI imaging techniques

Diffusion tensor imaging (DTI), volumetric brain imaging, and susceptibility-weighted imaging (SWI) are three techniques that can assess structural changes following TBI. DTI allows the mapping of white matter tracts by evaluating the anisotropic, or preferential, Brownian motion along the tract; this can generate apparent diffusion coefficient (ADC), mean diffusivity, and fractional anisotropy (FA) measurements [55]. FA ranges from 0, implying complete isotropy (unrestricted motion) of water molecules, such as in CSF, to 1, implying complete anisotropy (restricted motion), such as nerve fiber tracts. Most studies on DTI often focus on these quantitative properties in a particular voxel or region of interest (ROI), which contain multiple white matter tracts with differing trajectories, making inferences about individual white matter tracts difficult [56]. DTI has been successfully applied in preoperative planning in epilepsy and brain tumor surgery [57, 58]. In comparison, volumetric brain imaging is generated through 3D T1-weighted imaging sequences, often a standard MRI brain imaging sequence; through these images, gray and white matter may be separated and analyzed [55].

Studies of DTI in mTBI are heterogeneous in methodology, assessing different time points postinjury, comparator groups (controls vs. preinjury baseline), and anatomical ROIs. A review of 100 studies assessing DTI found a reduction in FA in TBI independent of the severity and timing since the injury. Anatomical regions most implicated were the corpus callosum, frontal lobes, internal capsule, and cingulum, which are high FA tracts, and thus possibly more likely to demonstrate a statistically significant change in TBI [59]. Seven of the eight included SRC studies in this review concurred with these DTI findings. Another review of DTI in PCS found that reduced FA and increased mean diffusivity (MD) and radial diffusivity (RD) were associated with the development and severity of PCS [60]. The corpus callosum was again found to be the most affected brain region. DTI changes have also been found in youth American football players with subconcussive head impacts, with a significant correlation between head impacts and reduced FA in two regions (left inferior fronto-occipital fasciculus (IFOF) and the right superior longitudinal fasciculus (SLF) terminal), with greater significance found at the terminals of gray and white matter intersection [61].

In comparison, studies on volumetric brain analysis in mTBI and SRC have consistently shown reductions in brain volume. One study comparing 28 patients one-year following mTBI and 22 controls found a global brain atrophy in the mTBI group greater than the control group, with the bilateral anterior cingulate and left cingulate gyrus isthmus white matter tracts showing a significant reduction in volume

loss, as well as the right precuneal gray matter. Reduction in neurocognitive memory and attention assessments was also correlated with volume loss in the bilateral rostral anterior cingulum white matter, while left cingulate gyrus isthmus correlated with clinical scores of anxiety and postconcussive symptoms [62]. In another study of 50 patients with mTBI, 19 of whom had a posttraumatic headache, those with headaches had significantly reduced gray matter volume in the right anterior parietal and left temporo-opercular regions at 18 months compared to those without posttraumatic headache. There were also several regions of decreased gray matter clusters compared to controls [63]. Volumetric studies in athletes have implicated volume reduction in the thalamus [64] and hippocampus [65]. However, interestingly, a study assessing former college American football players at early midlife (with a mean age of 37.9) found that although repetitive head injury impacts were associated with smaller hippocampal volume, those with professional/graduate degrees did not have a statistically significant reduction in hippocampal volume [66]. This emphasizes the moderating impact of factors such as age and educational attainment, so volumetric studies should be interpreted within this context. Moreover, as in DTI, the comparator population is important, given that there may be normal variation with volumetric brain structures which may not be clinically relevant. Comparison of structural changes in the same athlete pre- and postconcussion appears to be more sensitive in identifying abnormalities [67].

Susceptibility-weighted imaging (SWI) is an MRI technique that is useful for detecting microhemorrhages. Alongside CT, this has been applied in TBI in the diagnosis of diffuse axonal injury [68]. Although noted not to be in a sports-related concussion population, the incidence of microhemorrhages is greater than may first be perceived; in an American cohort study of patients presenting to level 1 and 2 trauma centers with head injury, of which 83% had mTBI, traumatic microhemorrhages were found in 31%. Those with traumatic microhemorrhage were twice as likely to have a disability at 30- and 90-days postinjury, defined as Glasgow Outcome Score ≤ 6 [69]. Another study following up 30 mTBI patients up to 1 year following their injury found that the presence of microhemorrhages showed worse performance in several cognitive tests in the acute and chronic phase stages, as well as higher symptom severity in the postconcussion symptom scale (PCSS) at 12 months postinjury [70]. However, like other methods of structural MRI evaluation, SWI needs to be considered within the baseline of the patient, as subclinical vasculopathy and amyloid angiopathy may also cause SWI abnormalities. Most literature does not have pre-mTBI imaging; therefore, this may be a confounding factor that may explain some of the abnormalities found. Therefore it may be unclear to what extent such abnormalities were present preinjury, although most athletes are usually younger than the expected age cohort to have such vascular abnormalities [55].

2.3.2 Metabolic MRI imaging: MR spectroscopy

Magnetic resonance spectroscopy (MRS) may act as a 'virtual biopsy' to identify metabolic changes in regions of interest. Commonly studied markers include N-acetyl-aspartate (NAA), a neuronal marker; choline (Cho), a measure of cell membrane turnover; creatine (Cr), a marker of energy metabolism; myoinositol, a glial marker; and glutamate and glutamine (Glx), excitatory neurotransmitters [55]. Several studies have found a decrease in NAA in mild TBI but were equivocal about Cho [54]. In a longitudinal study with serial MR spectroscopy up to 6 months postinjury in 43 patients with mTBI, there was a significantly reduced Cho/Cr ratio

in the thalamus and centrum semiovale in the late subacute stage (mean 37 days postinjury); high Cr in the early subacute stage (mean 5 days postinjury) was positively associated with some neuropsychological metrics at the chronic stage (mean 195 days postinjury), suggesting a possible role in predicting functional outcome [71]. These findings are contrary to our understanding of Cr in metabolic pathways, as this marker is expected to decrease in metabolic crisis states such as SRC. Finally, an MRS study in former NFL American football players found significantly positive correlations between glutamate, glutathione, and myoinositol in the anterior cingulate gyrus and behavioral/mood symptoms, while repetitive head injury was associated with lower parietal white matter creatine [72]. This suggests that repetitive head injury in SRC may lead to reduced cellular energy metabolism, while neuroinflammation may underpin behavioral/mood symptoms.

2.3.3 Perfusion-based MRI imaging: Perfusion-weighted imaging and functional MRI

Perfusion-weighted imaging and functional MRI (fMRI) are two further techniques that have been studied in the SRC literature. Both assess blood flow to regions of the brain to a certain extent, particularly during tasks. The results of these techniques have been mixed, possibly due to the complexity of structural and neurophysiological changes following injury [55]. In a meta-analysis of task-related fMRI studies, the most consistent finding in mTBI was reduced activation in the right middle frontal gyrus, as well as decreased activation in the prefrontal region being associated with cognitive impairment, which may be a result of neuronal injury to the cortex or disruptions to structural connectivity [73]. Within the SRC literature, abnormal resting state fMRI connection cerebellar lobule 5 was found in retired rugby league players [74], while another study of 13 retired NFL players found increased activation of DLPFC and reduced connectivity in the dorsal frontoparietal network while examining executive function [75].

With respect to perfusion imaging, a study of 24 athletes with concussion, followed up to 1 year after return to play, found that cerebral blood flow was elevated in the superior frontal gyrus in the early symptomatic phase, with reduced blood flow in the middle frontal and temporal regions at 1 year [76]. This gives an indication of longer-term changes in the brain following concussion, although the significance of this is currently unclear. Another perfusion study in a group of 15 teenage athletes up to 6 weeks postconcussion found increased cerebral blood flow in the left dorsal anterior cingulate cortex (ACC) and insula, which persisted at the left ACC at 6 weeks. CBF was also higher in the left ACC in athletes with persisting symptoms at 6 weeks postinjury [77]. However, another study in 24 concussed collegiate American football players showed highly significantly (<0.01) reduced CBF in the left inferior parietal lobule (IPL), right middle frontal gyrus (MFG), and thalamus in concussed athletes 24-48 h postinjury compared to controls [78]. There were also correlations between clinical and neuropsychological assessments and CBF in numerous brain regions. Finally, a study of concussed American football players against controls demonstrated a significant reduction in CBF at 8 days compared to 24 hours posttrauma in multiple frontal and temporal lobe regions [79], suggesting physiological changes persisted beyond the point of clinical recovery.

In summary, there is an ever-increasing amount of data on MRI imaging in SRC, with some techniques such as DTI analysis of the corpus callosum and fMRI of the right middle frontal gyrus being consistently demonstrated as abnormal in the

aggregated mTBI/SRC literature. However, data on other methods have been mixed, and imaging studies confounded the range of normal variance in neuroimaging techniques. Therefore larger, longitudinal studies with baseline imaging are required to better establish the causative changes in the brain in SRC.

2.4 Pitchside and neuropsychological evaluation

Neuropsychologists have become increasingly integrated in the assessment of SRC, and indeed most of the present protocols of SRC management center on detecting cognitive deficits resulting from SRC and monitoring the athlete's recovery. Barth and colleagues first demonstrated using baseline and postconcussion neuropsychological testing that college American football players had measurable cognitive deficits following concussion, which resolved within 5-10 days postconcussion [80]. This progressed to the development of the computerized Immediate Postconcussion Assessment Cognitive Test (ImPACT) [81], which has dominated the sports neuropsychology literature since. Neuropsychological measurements are often used within return-to-play protocols at both the grassroots and professional levels [82].

The traditional model of neuropsychological testing requires 4-6 hours, which is impractical for many athletes, leading to the development of composite assessment batteries, the most prominent of which is the Penn State battery [83], forming the basis of many contemporary concussion protocols. Furthermore, along with the ImPACT assessment, there has been a proliferation of computer neurocognitive assessment devices (CNADs), providing greater access to athletes but at risk of being affected by factors such as response validity, athlete background, or psychometrics, leading to discrepancies with their paper counterparts [84, 85]. To that effect, American neuropsychology bodies released a position statement outlining the best practice for the use of CNADs [86].

Although not strictly a neuropsychological tool, the Sports Concussion Assessment Tool, now in its 6th iteration, has consistently demonstrated the highest sensitivity and specificity out of all pitchside tools in diagnosing SRC (sensitivity 0.83-0.96, specificity 0.81-0.91) [81, 87]. Iterations of the SCAT have included other testing elements with proven efficacy, such as the PCSS, BESS, tandem gait test, and Standard Assessment of Concussion measures. It has been recommended by expert working groups to be used in athletes >13 years of age, with the largest effect sizes occurring <24 hours of injury [81]. The King-Devick test, a measure of visual pathways responsible for planning, initiation, and execution of coordinated saccades/antisaccades, reading, and rapid number naming, has been posited as a useful adjunct alongside the SCAT [88]. While the SCAT may require trained professionals to administer components (e.g., GCS), the King-Devick test has found no difference in scoring between nonprofessionals and professionals [81]. However, a recent meta-analysis found that it has a relatively lower sensitivity (0.77) and specificity (0.82) compared to SCAT, although it noted the quality of evidence to be low, and the test to be predominantly used in male athletes <25 years old, potentially limiting its applicability to other athlete groups [89].

Emerging pitchside assessments include eye tracking and head impact sensors, among others. However, the vestibular/ocular motor screening (VOMS) tool has shown the most promise thus far. This measures response to vestibular/ocular provocation in five domains (convergence, horizontal and vertical saccades, smooth pursuit, horizontal and vertical vestibulo-ocular reflex, and visual motion sensitivity); before the assessment and after each domain, participants are asked about changes in four symptoms (headache, dizziness, nausea, and fogginess) on a 10-point rating scale.

There have been FDA-approved eye-tracking devices that may partially or wholly automate this process, which may be useful in the SRC setting where athletes may not undergo specialist concussion clinical assessment immediately following concussion [90]. It showed high internal consistency (Croenbach's alpha 0.91), with each domain being significantly greater in concussed participants compared to controls. Using a composite model of visual motion sensitivity, vestibulo-ocular reflex convergence distance, the AUC was 0.89 [91]. This has been externally validated in identifying concussions in college athletes within 3 days of injury [92]. It has also been found to have a large effect size in a large cohort of concussed collegiate athletes. However, it had moderate test-retest reliability when comparing preseason baseline to the acute post-concussion phase, alongside other pitchside measurements such as the ImPACT and SCAT3. This suggests that preseason baseline SRC assessments may not be important in identifying clinically significant differences in SRC assessments postconcussion [93].

2.5 Conclusions

Sports-related concussion remains, at present, a clinical diagnosis, with clinical assessment tools such as the SCAT being used as adjuncts to assist with the diagnosis. This has been shown to have high sensitivity and specificity, but there is a need to explore different modalities for diagnosing and progressing sports-related concussions. It is clearly a heterogeneous condition, with some markers such as S100**β** and tau being elevated after physical activity and neuroimaging changes, possibly reflecting preinjury or normal variant characteristics. GFAP, tau, and NFL were elevated in athletes who had a prolonged return to play. However, more work is required to monitor the physiological and neuroimaging changes following SRC, their correlation with symptoms and the decision to return to play. This should be done in collaboration between healthcare professionals, athletes, and sporting organizations, such as with the CARE consortium [32]. A future assessment of SRC and return to play may incorporate multi-modality techniques involving validated biological, neuroimaging, and neuropsychological measures. A future assessment of SRC may involve a multimodal assessment involving biological, imaging, and neuropsychological measures [94], and we would encourage future research in the field to be driven toward this.

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